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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/407,430	09/29/1999	HOWARD J. WORMAN	0575/54805	2750

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EXAMINER
NGUYEN, QUANG

ART UNIT	PAPER NUMBER
1636	19

DATE MAILED: 06/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/407,430	WORMAN ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,7,10,11 and 44-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,7,10-11 and 44-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

The request filed on April 08/2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/407430 is acceptable and a CPA has been established. An action on the CPA follows.

Applicants' amendment filed 2/21/02 in Paper No. 15 has been entered. Accordingly, claims 1, 3, 5, 7, 10-11 and 44-49 are pending in the present application, and they are examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 5, 7, 10-11 and 44-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte*

Forman, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Claims 1, 3, 5, 7 and 10-11 are directed to a method of treating or preventing hepatitis C virus (HCV) infection in a subject comprising administering an effective amount of an E_0 protein having amino acids 1-120 of SEQ ID NO:1 to the subject, wherein the E_0 protein is capable of inhibiting the attachment of hepatitis C virus onto cells by specifically binding to the hepatitis C virus envelope E2 protein so as to treat or prevent hepatitis C virus infection.

Claims 44-49 are drawn to a method of preventing attachment of hepatitis C virus onto a cell, which comprises contacting the cell with an effective amount of an E_0 protein having amino acids 1-120 of SEQ ID NO:1 to the subject, wherein the E_0 protein is capable of inhibiting the attachment of hepatitis C virus onto cells by specifically binding to the hepatitis C virus envelope E2 protein.

The specification teaches by exemplification that using the yeast two hybrid assay, two clones encoding a portion of a protein were selected from a library of human liver Matchmaker cDNA for interacting with a portion of hepatitis C virus E2 lacking its most hydrophobic, carboxyl terminal domain. The sequence of the encoded portion of a protein, referred to as E_o protein, has the amino acid sequence of SEQ ID NO: 1. Furthermore, the specification teaches that the encoded amino acid sequence containing amino acid residues 1-120 of SEQ ID NO:1 (or E_o1 protein) is also capable of binding to the portion of hepatitis C virus E2 as does the E_o protein of SEQ ID NO:1, although at a relatively weaker binding affinity (See specification, pages 18-20).

The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant claimed invention which is drawn to methods of treating or preventing hepatitis C virus infection or preventing attachment of hepatitis C virus onto a cell in a subject using an effective amount of E_o protein having amino acids 1-120 of SEQ ID NO:1.

The instant specification is not enabled for the claimed invention because it fails to provide any guidance regarding the use of any effective amount of an E_o protein having amino acids 1-120 of SEQ ID NO:1 to treat or prevent hepatitis C infection in any subject or to prevent the attachment of hepatitis C virus onto a cell in a subject. The specification fails to teach or demonstrate a correlation or a nexus between the binding interaction of the E_o protein having SEQ ID NO:1 and the E_o1 proteins with a portion of the hepatitis C virus E2 envelope protein observed via the yeast two hybrid assay with any of the therapeutic effects contemplated by the claimed invention which comprise the inhibition of HCV replication, stopping or delaying the progression of liver disease in a subject or to prevent attachment of hepatitis C virus onto a cell in a subject. Apart from the yeast two hybrid assay system, there is no evidence of record indicating or suggesting that a similar interaction between E_o or E_o1 protein with a portion of the hepatitis C virus E2 envelope protein would also occur in other non-yeast biological systems, let alone for attaining the desired results contemplated by Applicants. Rosa et al. (Proc. Natl. Acad. Sci. 93:1759-1763, 1996; IDS) have reported that in contrast to E2 protein expressed in mammalian cells, E2 protein expressed in yeast or insect cells are not capable of binding to human cells (see Fig. 1), nor do they elicit neutralizing

antibodies to protect chimpanzees from primary infection by an homologous hepatitis C isolate (page 1761, col. 2, top of first full paragraph). Thus, it is unclear about the significance of the interaction between E_o or E_o1 protein with a portion of a hepatitis C virus E2 envelope protein solely in yeasts as reported in this application to the desired results contemplated by Applicants to be attained in a subject. Furthermore, in a review on the yeast two-hybrid system (Current Opinion in Biotechnology 6:59-64, 1995), Luban et al. have noted that a major problem associated with two-hybrid screens is the appearance of false-positives inherent in any transcriptional readout, and strong evidence for a direct interaction between the proteins should be provided in a biochemical assay, preferably one should show that the two proteins co-precipitate in their native context (page 62, col. 1, second full paragraph). Luban et al. further stated "The last issue, which is usually the most difficult aspect of working with the two hybrid system, is that one must demonstrate the functional significance of the protein-protein interaction that one has discovered" (page 62, col. 1, top of the third full paragraph). Since the prior art at the filing date of the present application does not provide any guidance regarding to the use of any effective amount of E_o or E_o1 protein to attain the results contemplated by Applicants in a subject, it is incumbent upon the instant specification to do so. Particularly, at the filing date of the present application, standard treatments for patients infected with hepatitis C include therapies using recombinant alpha interferon alone or in combination with the nucleoside analogue Ribavirin, whose actions are not mediated via inhibiting the attachment of hepatitis C virus onto cells (Gish, Seminars in liver disease 19 (S1): 35-47, 1999; Cited previously). Since the

physiological art is recognized as unpredictable (MPEP 2164.03), and as set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictagle factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Accordingly, with the lack of guidance provided by the instant specification, it would have required undue experimentation for one skilled in the art to make and use the instant claimed invention.

With respect to the embodiment of preventing hepatitis C virus infection or preventing attachment of hepatitis C virus onto a cell in a subject using an effective amount of an Eo protein having amino acids 1-120 of SEQ ID NO: 1 as encompassed by the instant claims, the specification is not enabled for such a claimed invention. At the filing date of the present application, it is already known in the art that other polypeptides such as the CD81 protein (Abrignani et al., WO 99/18198; see page 2, lines 18-25; Cited previously), annexin V, tubulin, apolipoprotein B (Maertens et al., WO 99/24054; see abstract; Cited previously), as well as endogenous host proteins such as the chaperone protein calnexin and lactoferrin are also capable of binding at least to the hepatitis C virus envelope protein E2 (Maertens et al., WO 99/24054; page 2, lines 12-29). However, the potential therapeutic values of these proteins for treating or for preventing HCV infection in a subject remain to be determined or investigated because the mechanism by which HCV enters target cells remains unknown (Flint et al., J. Virol.

73:6782-67900, 1999; page 6782, column 2, last three lines). Flint et al. stated that "Clearly, it will be important to demonstrate whether CD81, either alone or with additional factors, can function as the HCV receptor in allowing pseudotyped virus-cell attachment and entry. Since CD81 is so widely expressed, it is unlikely to be the sole factor determining HCV liver tropism" (page 6789, column 1 lines 1-6). Since it is unclear how hepatitis C virus enters target cells in the art at the filing date of the present application, then how the simple binding of E_o or E_o1 protein with a portion of a hepatitis C virus E2 envelope protein in a yeast two-hybrid assay can be reasonably extrapolated to the prevention of HCV infection or HVC attachment onto any cell in a subject as claimed. Additionally, even suppose that the simple binding of any protein with the E2 envelope protein is a reasonable correlation for preventing attachment of HCV virus onto cells in a subject, and thereby treating or preventing HCV infection, then why CD81, annexin V, tubulin, apolipoprotein B as well as calnexin and lactoferrin have not been routinely used in the treatment or therapy for patients infected with HCV? With the absence of sufficient guidance provided by the instant specification, particularly with the lack of any *in vivo* example (part of guidance), it would have required undue experimentation for a skilled artisan to make and use the presently claimed invention.

With respect to the use of an E_o protein having amino acids 1-120 of SEQ ID NO: 1 in the method as claimed, it is unclear whether the E_o protein is capable of exhibiting an effective binding affinity for the full-length E2 envelope protein presented on the surface of the hepatitis C virus, usually in complexes with other viral envelope components, such as the E1 envelope protein, such that it can disrupt such complexes

and thereby preventing the attachment of hepatitis C virus onto any cell or preventing or treating hepatitis C virus infection in a subject. Gish noted that the standard management of chronic HCV infection is complicated by various factors, including: the rapid mutation rate of the HCV genome, particularly the hypervariable region, the lack of neutralizing antibodies to HCV gene products, and the lack of sequence homology (less than 72%) among various subtypes of HCV (page 36, column 1, first full paragraph, line 8 continues to the first paragraph on column 2). It is also thought that the binding of E2 to target cells mostly involves the highly variable amino terminus of E2, the hypervariable region I (Maertens et al., WO 99/24054; page 2, lines 12-17). As such, it is unclear whether E_o or E_o1 protein, is capable of binding efficiently *in vivo* to the highly variable region of E2 in any HCV subtype such that it can inhibit the attachment of HCV onto any cell and thereby treating and preventing HCV infection in a subject. Therefore, given the complete lack of guidance provided by the instant specification regarding to the effective *in vivo* use for any E_o protein that is capable of inhibiting the attachment of hepatitis C virus onto cell so as to treat and prevent HCV infection in a subject, it would have required undue experimentation for a skilled artisan to make and use the claimed invention.

The instant claims encompass any route of administering the E_o protein into a subject to treat or prevent hepatitis C infection or preventing attachment of hepatitis C virus onto a cell in a subject. However, the instant specification fails to provide any relevant information regarding to the *in vivo* stability of the E_o protein utilized or how to overcome random degradation of the administered E_o protein in a treated host and more

importantly how to target the E_o protein to a desired tissue or organ in an effective amount by any means of delivery such that any therapeutic effects (treatment and prevention) or preventing attachment of hepatitis C virus onto any cell in a subject as contemplated by Applicants could be attained. Again, in the absence of any guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the instant claimed invention.

Accordingly, due to the lack of guidance provided by the specification regarding to the issues set forth above, the state of the art on treatment or prevention of hepatitis C at the effective filing date of the present application, the unpredictability of the physiological art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant claimed invention.

Responses to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on 2/21/02 in Paper No. 15 in Paper No. 15 (pages 5-9) have been fully considered.

Applicants mainly argued that in light of the study of Rosa et al. (PNAS 93:1759-1763, 1996; Exhibit 14) indicating that E2 envelope protein of HCV can bind to the plasma membranes of cells and this action of E2 mediates entry of the virus into the cells, together with the study of Yi et al. (Virology 231: 119-129, 1997, Exhibit 17) showing that E2 and E1 envelope proteins form a heteromeric complex and this complex is necessary for virus binding to the cells and entry into the cells, it is therefore reasonable to expect that the E_o protein of the present invention to block HCV

attachment and entry into cells due to its capability to bind E2 envelope protein. Applicants further argued that antibodies that bind to E2 have been shown to prevent HCV infection *in vivo* as evidenced by the teachings of Rosa et al. and Flint et al.. Therefore, by binding to E2 envelope protein, the Eo protein is reasonably expected to block HCV attachment and entry into cells. Examiner respectfully finds Applicants' arguments to be unpersuasive for the reasons discussed below.

Examiner would like to state that the binding of Eo with E2 envelope protein shown in a yeast two-hybrid assay in the present application is not correlated or equivalent to the action of neutralizing antibodies specific against E2 protein as taught by Rosa et al. or Flint et al., and therefore the desired results contemplated by Applicants would not be reasonably expected to be obtained. This is because: (a) There is no evidence of record indicating or suggesting that Eo binds to the E2 envelope protein at the same epitopes as the reported neutralizing antibodies. Which particular amino acid residues on the E2 envelope protein being recognized by the Eo protein of the presently claimed invention? Certainly, the whole amino acid sequence of residues 384 to 661 in E2 envelope protein does not constitute a neutralizing epitope (please check the definition of an epitope). Without knowing or teaching this relevant information, then how can one assert or certain that Eo protein bind to the same neutralizing epitopes recognized by antibodies to prevent HCV attachment or entry to cells in a subject and thereby treating or preventing HCV virus infection? (b) It should be further noted that the interaction between Eo or Eo1 protein with an E2 envelope protein reported in the present application was observed in yeast cells. However, Rosa

et al. (Proc. Natl. Acad. Sci. 93:1759-1763, 1996; IDS) have reported that in contrast to E2 protein expressed in mammalian cells, E2 protein expressed in yeast or insect cells are not capable of binding to human cells (see Fig. 1), nor do they elicit neutralizing antibodies to protect chimpanzees from primary infection by an homologous hepatitis C isolate (page 1761, col. 2, top of first full paragraph). Thus, it is unclear about the significance of the interaction between E_o or E_o1 protein with a portion of a hepatitis C virus E2 envelope protein solely in yeasts as reported in this application to the desired results contemplated by Applicants to be attained in a subject. Furthermore, in a review on the yeast two-hybrid system (Current Opinion in Biotechnology 6:59-64, 1995), Luban et al. have noted that a major problem associated with two-hybrid screens is the appearance of false-positives inherent in any transcriptional readout, and strong evidence for a direct interaction between the proteins should be provided in a biochemical assay, preferably one should show that the two proteins co-precipitate in their native context (page 62, col. 1, second full paragraph). Luban et al. further stated "The last issue, which is usually the most difficult aspect of working with the two hybrid system, is that one must demonstrate the functional significance of the protein-protein interaction that one has discovered" (page 62, col. 1, top of the third full paragraph). (c) There is also no evidence of record (*in vitro* or *in vivo*) indicating that the E_o protein of the present invention can disrupt the E1 and E2 heteromeric complex (already formed complex) that is thought to be necessary for HCV virus binding and entry to the cells as taught by Yi et al. and asserted by Applicants. Unlike the simplified situation presented by Applicants that upon binding to the E2 envelope protein by the Eo protein of the

present invention, the E2 protein can not bind to the E1 protein to form the heterodimeric complex, it should be noted that the claimed method is not a simple *in vitro* binding method by mixing various components in a test tube. The endogenous E1/E2 heteromeric complex is already present in the HCV virus. As such, how can a simple application of Eo protein of the instant invention in a subject disrupt the E1/E2 heteromeric complex to prevent HCV attachment to a cell or prevent or treating HCB infection in a subject? Particularly, critical information regarding to the biochemical binding properties of the Eo protein to a mammalian expressed E2 protein has yet been determined.

Therefore, with the lack of sufficient guidance provided by the present disclosure, particularly in the absence of any reasonable correlated *in vivo* example for the methods as claimed, the unpredictability of the physiological art as well as the state of the art on the treatment or preventing HCV in a subject, it would have required undue experimentation for a skilled artisan to make and use the instant claimed invention.

Accordingly the amended claims 1, 3, 5, 7, 10-11 and 44-49 remain rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth above.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Irem Yucel, Ph.D., at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636.

Quang Nguyen, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER